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(54) **Vitamin D3 derivatives having a substituent at 2-position.**

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Description

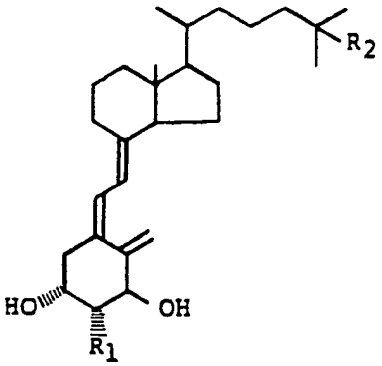
The present invention relates to novel vitamin D_3 derivatives that have calcium control action and the ability to induce differentiation in tumor cells and which are useful both as antitumor agents and as medicines for the treating calcium dysbolism-caus d dis ases such as osteoporosis and osteomalacia. More specifically, the present invention relates to such vitamin D_3 derivatives having a substituent at 2β-position.

While many vitamin D_3 compounds are known in the art, they are generally classified as naturally occurring vitamin D_3 metabolites (e.g. 25-hydroxy vitamin D_3, 1α,25-dihydroxy vitamin D_3 and 1α,24,25-trihydroxy vitamin D_3) and their synthetic analogs (e.g. 1α-hydroxy vitamin D_3, 1α,24-dihydroxy vitamin D_3, and a variety of fluorinated vitamin D_3 compounds) see for example WO—A—81/03 023 and WO—A—82/02 893. Among these known vitamin D_3 compounds, the naturally occurring 1α,25-dihydroxy vitamin D_3 and a synthetic analog wherein the side chain attached to 17-position of vitamin D_3 is fluorinated such as 24,24-difluoro-1α,25-dihydroxy vitamin D_3 have a strong calcium control action and are useful in treatment of various bone disorders.

In the US—A—4,011,250 the synthesis of 1α,2α dihydroxy-cholecaliciferol which has improved vitamin D activity is disclosed.

While studying a variety of vitamin D_3 derivatives, the present inventors have found that certain vitamin D_3 derivatives having a substituent at 2-position, especially at 2β-position, exhibit a strength comparable to 1α,25-dihydroxy vitamin D_3 in terms of the *in vivo* calcium control action.

The 1α-hydroxy vitamin D_3 derivative having a substituent at 2β-position is represented by the following formula (I):



(I)

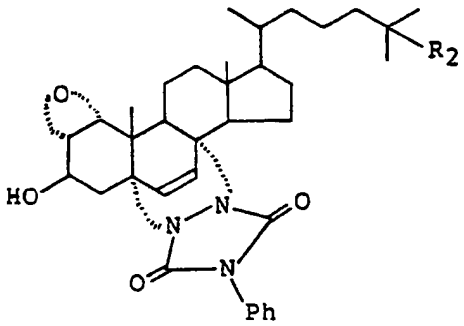
where R_1 is a hydroxyl group, an amino group or the group OR' (where R' is a lower alkyl group which may or may not be substituted by a hydroxyl group, a halogen atom, a cyano group, a lower alkoxy group, an amino group or an acylamino group); and R^2 is a hydrogen atom or a hydroxyl group.

Examples of the lower alkyl group represented by R' in formula (I) are branched- or straight-chain alkyl groups having 1 to 7 carbon atoms, and these alkyl groups may be substituted at a desired position by a hydroxyl group, a halogen such as bromine or chlorine, a cyano group, a lower alkoxy group having 1—3 carbon atoms, an amino group, or an acylamino group.

The 1α-hydroxy vitamin D_3 compounds of the formula (I) are novel and may be synthesized by the following procedures:

1) a cyclized adduct of 1,5,7-cholestatrien-3β-ol and 4-phenyl-1,2,4-triazoline-3,5-dione is prepared from cholesterol or 25-hydroxy-cholesterol according to the description in JP—A—84555/1975 and 84560/1975;

2) the cyclized adduct is converted to a 1α,2α-epoxide (compound 1) having the formula shown below:

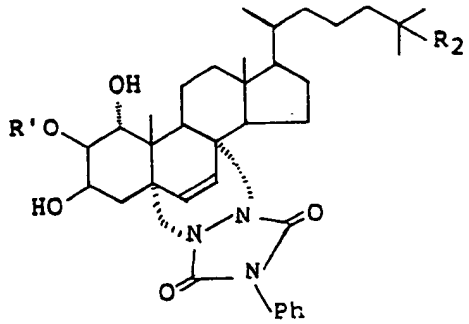


(1)

(wher R_2 is a hydrogen atom or a hydroxyl group; and Ph is a phenyl group);

3) the epoxide (compound 1) is reacted with a nucl philic r agent, such as an alcohol, f th formula:

R'OH (where R' is the same as defined above) in an inert solvent in the presence of an acid catalyst such as p-toluenesulfonic acid to obtain a compound of formula (II):



(II)

(where R', R_2 and Ph are respectively the same as defined above); and

4) the compound (II) is subjected to the process shown in JP—A—84555/1975 that consists of elimination of the triazoline-3,5-dione ring, exposure to radiation and isomerization, whereby the compound of formula (I) is obtained.

By reacting the epoxide (compound 1) with water rather than an alcohol as a nucleophilic reagent, a compound (II) having a hydroxyl group at 2-position is obtained. If sodium azide is used as the nucleophilic reagent, a compound (II) having an azido group at 2-position is obtained. These compounds are subjected to step 4) after elimination of the triazoline-3,5-dione ring, the resulting provitamine D_3 derivative is irradiated with ultraviolet radiation and the irradiated derivative is subjected to thermal isomerisation to obtain compounds of formula (I) wherein R_1 is a hydroxyl group and an amino group, respectively. The azido group at 2-position of compound (II) may be converted to an amino group by subjecting said compound to reduction with lithium aluminum hydride simultaneously with the elimination of the 1,2,4-triazoline ring.

Pharmacological Actions of Compound (I):

The compounds of the present invention were found to have the calcium control action and the ability to induce differentiation in tumor cells by the following experiments.

(A) Calcium control action

i) Male weanling Spraque Dawley rats weighing 45—50 g were fed Diet 11 and deionized water under an incandescent lamp for 3 weeks. The compound of the present invention (as prepared in Example 4), and a control 1α,25-dihydroxy vitamin D_3 (1α,25-$(OH)_2D_3$), which were respectively dissolved in ethanol, were administered intravenously into the animals. The animals were the starved for 24 hours and blood samples were drawn from the heart of each rat. Plasma was isolated from each blood sample and the contents of calcium and inorganic phosphorus were measured by the OCPC method described in Am. J. Clin. Path., *45*, 290 (1966) and Biochem. J., *65*, 709 (1957). The results are shown in Table 1.

Table 1

Compound	Dose	Calcium in plasma (mg/dl)	Inorganic P in plasma (mg/dl)
EtOH only	0.5 mg/kg	4.796±0.207	9.403±1.517
Compound of Example 4	6.25 μg/0.5 ml/kg	5.916±0.323***	8.533±0.687
	12.5 μg/0.5 ml/kg	6.058±0.551***	8.503±1.387
1α,25-$(OH)_2$-D_3	1.25 μg/0.5 ml/kg	5.463±0.290**	7.561±0.477*
	2.5 μg/0.5 ml/kg	5.506±0.324**	9.066±1.906

***: $p<0.001$, **: $p<0.01$, *: $p<0.05$

ii) The same rats as described in i) were fed in the same manner as shown in i).

Two compounds of the present invention (as prepared in Examples 4 and 6) and two controls, 1α-hydroxy vitamin D_3 (1α-OH—D_3) and 25-hydroxy vitamin D_3 (25-OH—D_3), were administered orally to th rats for 5 consecutive days after being dissolved in triglyceride of medium-chain aliphatic acid (MCT). The rats given the last dose were starved for 24 hours and blood samples were drawn from the heart of each rat. The contents of calcium and inorganic phosphorus in plasma were measured by the same method as used in i). The results are shown in Table 2.

Table 2

Compound	Dose	Calcium in plasma (mg/dl)	Inorganic P in plasma (mg/dl)
MCT only	1 mg/kg	4.263±0.235	7.488±0.933
Compound of Example 4	6.25 μg/ml/kg	5.552±0.912*	8.713±1.648
Compound of Example 6	6.25 μg/ml/kg	8.093±0.648***	7.040±0.595
1α-OH-D_3	6.25 μg/ml/kg	4.798±0.582	7.776±0.682
25-OH-D_3	6.25 μg/ml/kg	5.682±0.364***	9.115±0.647**

***: $p<0.001$, **: $p<0.01$, *: $p<0.05$

(B) Induction of differentiation

i) Morphological change

Human promyelecytic leukemia cells (HL-60 cell line) were cultured in an RPMI—1640 medium supplemented with 10% heat-inactivated fetal calf serum under 5% CO_2/95% air at 37°C. To the so prepared medium, ethanol solutions of the compound obtained in Example 4 and control 1α-hydroxy vitamin D_3 were added in such a manner that the ethanol concentration in the liquid medium was 0.1%. Upon addition of the compound of Example 4 and the control, the HL—60 cells were found to differentiate into macrophage-like cells by morphological observation on 3 days. The percentage of the HL—60 cells that underwent differentiation was determined by counting their number.

At least 60% of the HL—60 cells treated with the compound of Example 4 in doses of the order of 10^{-6}—10^{-7} M were differentiated into macrophages, suggesting that said compound had a differentiation-inducing ability comparable to that of the control 1α-hydroxy vitamin D_3.

ii) NBT-reduced cell induction ability

To HL-60 cells, the compound prepared as in Example 4 was added for a period of 4—5 days. To the treated cells, TPA (12-O-tetradecanoylphorbol-13-acetate) and NBT (nitro blue tetrazolium) were added in respective final concentrations of 100 ng/ml and 0.1%. After standing for 20 minutes at 37°C, the percentage of the HL-60 cells that were differentiated into macrophages and reduced NBT to form formazan was determined. Both the compound of Example 4 and the control 1α-hydroxy vitamin D_3 exhibited a differentiation-inducing ability of 95% upward in a dose of 10^{-6} M.

The following examples are provided for the purpose of further illustrating the present invention and are by no means intended as limiting.

Example 1

Production of 1α-hydroxy-2β-methoxy vitamin D_3

a) Preparation of a Diels-Alder adduct of 2β-methoxy-5,7-chofestadiene-1α,3β-diol and 4-phenyl-1,2,4-triazoline-3,5-dione:

Five hundred milligrams (0.871 mmol) of the 1α,2α-epoxide compound 1 (R_2=H) was dissolved in 4 ml of dry tetrahydrofuran. To the solution, 10 ml of methanol and 35 mg (0.184 mmol) of p-toluene sulfonic acid were added and the mixture was heated under reflux for 5 hours. To the cooled mixture, ethyl acetate was added and the organic layer was washed successively with water, an aqueous solution of sodium hydrogencarbonate and water. After drying over magnesium sulfate, the solvent was distilled off. The residue was subjected to silica gel column chr mat graphy and eluted with chloroform containing 20% (v/v) acetone, producing 240.2 mg of the end compound.

NMR spectrum δ ($CDCl_3$): 0.80 (3H, s), 0.93 (3H, s), 3.43 (3H, s), 4.65 (1H, m), 6.07 and 6.33 (2H, AB, J=7.0 Hz), 7.28 (5H, m)

b) Preparation of 2β-methoxy-5,7-cholestadiene-1α,3β-diol:

A portion (229 mg, or 0.378 mmol) of the Diels-Alder adduct of 2β-methoxy-5,7-cholestadiene-1α,3β-diol and 4-phenyl-1,2,4-triazoline-3,5-dione prepared in a) was dissolved in 10 ml of dry tetrahydrofuran in an argon atmosphere and the solution was stirred at room temperature. After gradual addition of 60 mg (1.58 mmol) of lithium aluminum hydride, the mixtur was refluxed for 1 hour. To the ice-cooled reaction mixture, a saturated aqueous solution of sodium sulfate was added dropwise under agitation to quench excess lithium aluminum hydride. Th gel was removed by filtration und r sucti n and th tetrahydrofuran was distilled off. The residue was subjected to extraction with ethyl acetate, washed successively with dilute hydrochloric acid and water, and dried over magnesium sulfate. The solvent was distilled off and the residue was subjected to silica gel column chromatography. Upon elution with chloroform, 86 mg of the end compound was obtained.

UV spectrum λ_{max}^{EtOH} (nm): 292, 281, 270, 262 (sh)

c) Preparation of 1α-hydroxy-2β-methoxy vitamin D_3:

Eighty-six milligrams (0.20 mmol) of the 2β-methoxy-5,7-cholestadiene-1α,3β-diol obtained in b) was dissolved in 400 ml of ethanol of guaranteed quality. Under ice-cooling in an argon atmosphere, the solution was irradiated for 3 minutes by a 200 W mercury lamp through a Vycor® glass filter. After removal of the solvent under vacuum, the residue was dissolved in 10 ml of anhydrous tetrahydrofuran, and the mixture was heated under reflux for 1 hour. After cooling, the solvent was distilled off and the residue was subjected to column chromatography using Sephadex LH-20 (Pharmacia Fine Chemicals). Upon elution with a 65:35 mixture of chloroform and hexane, 14.0 mg of the end compound of the present invention was obtained as an oil.

UV spectrum λ_{max}^{EtOH} (nm): 263.5

Mass spectrum (m/e): 430 (M^+), 412, 398, 380 150

Example 2

1α-hydroxy-2β-ethoxy vitamin D_3

a) Preparation of Diels-Alder adduct of 2β-ethoxy-5,7-cholestadiene-1α,3β-diol and 4-phenyl-1,2,4-triazoline-3,5-dione:

A portion (506 mg, or 0.882 mmol) of the compound 1 (R_2=H) used in Example 1a) was dissolved in dry tetrahydrofuran (6 ml). To the solution, 12 ml of ethanol and 68 mg (0.357 mmol) of p-toluenesulfonic acid were added and the mixture was stirred for 2 days at room temperature. The stirred mixture was subsequently treated as in Example 1a) to give 172 mg of the end compound.

NMR spectrum δ ($CDCl_3$): 0.80 (3H, s)

b) Preparation of 2β-ethoxy-5,7-cholestadiene-1α 3β-diol:

The compound (172 mg, or 0.277 mmol) obtained in a) was dissolved in 15 ml of dry tetrahydrofuran in an argon atmosphere, and the solution was stirred at room temperature. After gradual addition of 154 mg (4.06 mmol) of lithium aluminum hydride, the mixture was refluxed for 1 hour. To the ice-cooled reaction mixture, a solution of sodium hydroxide was added dropwise under agitation to quench excess lithium aluminum hydride. The mixture was subsequently treated as in Example 1b) to give 60.1 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 293, 281, 271, 262 (sh)

NMR spectrum ($CDCl_3$): 0.62 (3H, s), 0.81 (3H, s), 1.05 (3H, t), 3.68 (2H, q), 5.31 and 5.67 (2H, AB, J=6.0Hz)

c) Preparation of 2β-ethoxy-1α-hydroxy vitamin D_3:

The 2β-ethoxy-5,7-cholestadiene-1α,3β-diol (60.1 mg, or 0.135 mmol) obtained in b) was treated as in Example 1c) to obtain 10.5 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 264

Mass spectrum (m/e): 444 (M^+), 426, 398, 380, 150

Example 3

1α-hydroxy-2β-isobutoxy vitamin D_3

The end compound was obtained by repeating the procedures of Examples 1a) thru c) xcept that the methanol used in Example 1a) was replaced by isobutyl alcoh l.

UV spectrum λ_{max}^{EtOH} (nm): 265

Mass spectrum (m/e): 416 (M^+), 398, 380, 150

Example 4

1α-hydroxy-2β-(2-hydroxyethoxy) vitamin D_3

a) Preparation of Diels-Alder adduct of 2β-(2-hydroxyethoxy)-5,7-cholestadiene-1α,3β-diol and 4-phenyl-1,2,4-triazoline-3,5-dione:

i) Using thylen glycol:

A portion (265 mg, or 0.462 mmol) of the compound 1 (R_2=H) used in Example 1a), 5 ml of dry tetrahydrofuran, 10 ml of ethylene glycol, and 37 mg (0.195 mmol) of p-toluenesulfonic acid were treated as in Example 1a) to obtain the end compound.

NMR spectrum δ ($CDCl_3$): 0.80 (3H, s), 0.90 (3H, s), 3.56 (2H, m), 3.74 (2H, m), 4.57 (1H, m), 6.09 and 6.29 (2H, AB, J=9.0 Hz), 7.29 (5H, m)

ii) Using a dioxolane compound:

A portion (102 mg, or 0.178 mmol) of the compound 1 used in Example 1a) was dissolved in 2 ml of dry tetrahydrofuran. To the solution, 1.0 ml (9.30 mmol) of 2,2-dimethyl-1,3-dioxolane and 100 µl of boron trifluoride etherate were added and the mixture was stirred for 20 hours at room temperature. After addition of ethyl acetate, the mixture was washed with water and dried over magnesium sulfate, followed by the distilling off of the solvent. The residue was subjected to silica gel column chromatography and eluted with chloroform containing 20% (v/v) acetone, producing 21.3 mg of the end compound which had the same physical data as those of the compound obtained in i).

b) Preparation of 2β-(2-hydroxyethoxy)-5,7-cholestadiene-1α,3β-diol:

A portion (398.5 mg, or 0.627 mmol) of the Diels-Alder adduct obtained in i) or ii) of a) above was treated as in Example 1b) using 40 ml of dry tetrahydrofuran and 333 mg (8.77 mmol) of lithium aluminum hydride. The end compound was obtained in an amount of 173.2 mg.

UV spectrum λ_{max}^{EtOH} (nm): 293.5, 281.5, 271, 262 (sh)

NMR spectrum ($CDCl_3$): 0.55 (3H, s), 0.83 (3H, s), 0.91 (6H, s), 5.30 and 5.62 (2H, AB, J=6.0Hz)

c) Preparation of 1α-hydroxy-2-(2-hydroxyethoxy) vitamin D_3

A portion (173 mg, or 0.376 mmol) of the 2β-(2-hydroxyethoxy)-5,7-cholestadiene-1α,3β-diol obtained in b) was treated as in Example 1c) to produce 39.9 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 262.5

Mass spectrum (m/e): 460 (M^+), 442, 398, 380, 150

FT—NMR spectrum ($CDCl_3$): 0.55 (3H, s), 0.86 (6H, d, J=6.6 Hz), 0.92 (3H, d, J=6.4 Hz), 3.33 (1H, dd), 3.65—3.90 (1H, m), 4.23 (1H, m), 4.37 (1H, d, J=8.4 Hz), 5.09 (1H, s), 5.49 (1H, s), 6.04 (1H, d, J=12.6 Hz), 6.37 (1H, d, J=12.6 Hz)

Examples 5 to 10

The compound listed below were obtained by repeating the procedures of Example 1a) thru c) except that the methanol used in Example 1a) was replaced by ethylene bromohydrin (Example 5), trimethylene glycol (Example 6), 4-methyl-1,4-pentanediol (Example 7), ethylene cyanohydrin (Example 8), water (Example 9) and 1,4-butanediol (Example 10).

Example 5

2β-(2-bromoethoxy)-1α-hydroxy vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 264

Mass spectrum (m/e): 446 (M^+-Br), 428, 400, 382, 134

Example 6

1α-hydroxy-2β-(3-hydroxypropoxy) vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 263

Mass spectrum (m/e): 474 (M^+), 456, 398, 380, 150

Example 7

1α-hydroxy-2β-(4-hydroxy-4-methylpentoxy) vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 263

Mass spectrum (m/): 517 (M^++1), 500, 398, 380, 150, 83, 59

Example 8

2β-(2-cyanoethoxy)-1α-hydroxy vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 262

Mass spectrum (m/e): 469 (M^+), 416, 398, 380, 150

Example 9

1α,2β-dihydroxy Vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 263

Mass spectrum (m/e): 416 (M^+), 398, 380, 150

Example 10

1α-hydroxy-2β-(4-hydroxybutoxy) vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 263.5

Mass spectrum (m/e): 488 (M^+), 470, 452, 150

Example 11

2β-(2-N-acetylaminoethoxy)-1α-hydroxy vitamin D_3

a) Preparation of 1α,2α-epoxy-5,7-cholestadiene-3β-ol:

A portion (2.05 g, or 3.57 mmol) of the compound 1 (R_2=H) used in Example 1a) was dissolved in 100 ml of dry dimethylformamide. After addition of 0.92 g (3.51 mmol) of triphenylphosphine, the solution was heated on a bath (90—100°C) for 10 hours under agitation. The reaction mixture was poured into ice water and subjected to extraction with ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate, followed by the distilling off of the solvent. The residue was subjected to silica g l column chromatography and eluted with chloroform containing 20% (v/v) acetone, thereby providing 1.29 g of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 290, 279, 269, 261 (sh)

NMR spectrum ($CDCl_3$): 0.63 (3H, s), 0.82 (3H, s), 0.91 (6H, s), 5.36 and 5.66 (2H, AB, J=6.0Hz)

b) Preparation of 2β-(2-N-acetylaminoethoxy)-5,7-cholestadiene-1α,3β-diol:

A portion (397 mg, or 0.996 mmol) of the 1α,2α-epoxy-5,7-cholestadiene-3β-ol obtained in a) was dissolved in 8 ml of dry tetrahydrofuran in an argon atmosphere. After addition of 2-N-acetylaminoethanol (3 ml), the mixture was stirred at room temperature. To the mixture, 0.2 ml of boron trifluoride etherate was added dropwise and the resultant mixture was stirred for 10 hours at room temperature, followed by refluxing for 7 hours. After cooling, ethyl acetate was added to the reaction mixture. The organic layer was washed with water and dried over magnesium sulfate, followed by the distilling off of the solvent. The residue was subjected to silica gel column chromatography and eluted with chloroform containing 20% (v/v) acetone, producing 32.6 mg of the end compound.

NMR spectrum δ ($CDCl_3$: CD_3OD=3:1): 0.64 (3H, s), 0.81 (3H, s), 0.90 (6H, s), 2.07 (3H, s), 3.34 (2H, m), 3.68 (2H, m), 5.28 and 5.60 (2H, AB, J=6.0Hz) 6.0 Hz)

c) Preparation of 2β-(2-N-acetylaminoethoxy)-1α-hydroxy vitamin D_3:

The 2β-(2-N-acetylaminoethoxy)-5,7-cholestadiene-1α,3β-diol (32.6 mg, or 6.50×10^{-2} mmol) obtained in b) was treated as in Example 1c) to obtain 6.96 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 262.5

Mass spectrum (m/e): 458 (M^+—CH_3CO), 440, 398, 383, 150, 43

Example 12

2β-amino-1α-hydroxy vitamin D_3

a) Preparation of Diels-Alder adduct of 2β-azido-5,7-cholestadiene-1α,3β-diol and 4-phenyl-1,2,4-triazoline-3,5-dione:

A portion (501 mg, or 0.873 mmol) of the compound 1 (R_2=H) used in Example 1a) was dissolved in 10 ml of dioxane in an argon atmosphere and the solution was refluxed. To the solution, 102 mg (1.57 mmol) of sodium azide as dissolved in 2.6 ml of water was added dropwise, and the resultant mixture was refluxed f r 10 hours. After co ling, the mixtur was subjected to extraction with thyl acetate, washed with water and dried over magnesium sulfate. After distilling off the solvent, the residue was subjected to silica gel column chr matography and eluted with chloroform containing 20% (v/v) acetone, to give 81.9 mg of the end compound.

IR spectrum vmax (cm^{-1}): 2250

NMR spectrum δ ($CDCl_3$): 0.81 (3H, s), 0.90 (3H, s), 6.15 and 6.33 (2H, AB, J=8.0 Hz), 7.33 (5H, m)

b) Preparation of 2β-amino-5,7-cholestadi ne-1α,3β-diol:

The Diels-Alder adduct (81.9 mg, or 0.133 mmol) obtained in a), 10 ml of dry tetrahydrofuran and 94 mg (2.48 mmol) of lithium aluminum hydride were treated as in Example 1b) to produce 39.5 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 292.5, 281, 271, 262 (sh)

IR spectrum vmax (cm^{-1}): 3500, 3320, 3210

NMR spectrum δ ($CDCl_3$:CD_3OD=3:1) 0.62 (3H, s), 0.83 (3H, s), 0.92 (6H, s), 5.37 and 5.59 (2H, AB, J=6.0Hz)

c) Preparation of 2β-amino-1α-hydroxy vitamin D_3:

The 2β-amino-5,7-cholestadiene-3β-ol (39.5 mg, or 0.0095 mmol) obtained in b) was treated as in Example 1c) to produce 6.28 mg of the end compound.

UV spectrum λ_{max}^{EtOH} (nm): 266

Mass spectrum (m/e): 416 (M^++1), 400, 382, 367, 134

Examples 13 and 14

Compound 1 (R_2=OH) which had been prepared from 25-hydroxycholesterol was treated as in Example 1a), b) and c) to produce the following compounds.

Example 13

1α,25-dihydroxy-2β-(3-hydroxypropoxy) vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 263

Mass spectrum (m/e): 490 (M^+), 472, 454, 59

Example 14

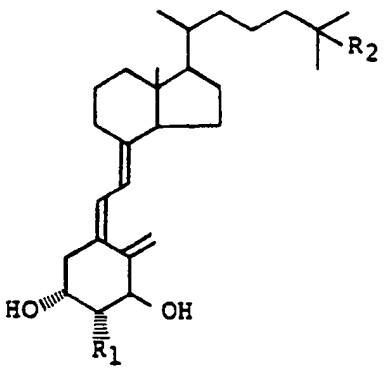
1α,25-dihydroxy-2β-(2-hydroxyethoxy) Vitamin D_3

UV spectrum λ_{max}^{EtOH} (nm): 262

Mass spectrum (m/e): 476 (M^+), 458, 440, 59

Claims

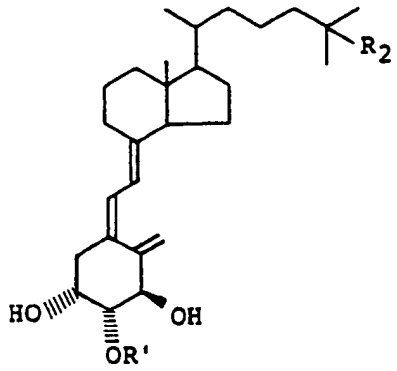
1. A 1α-hydroxy vitamin D_3 derivative of the formula I:



(I)

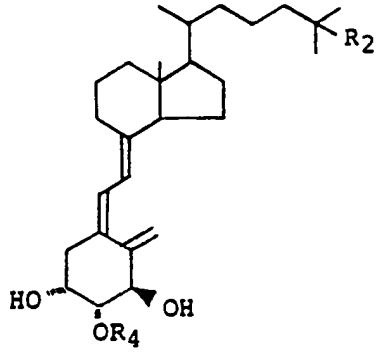
where R_1 is a hydroxyl group, an amino group or the group: OR' (where R' is a lower alkyl group having 1 to 7 carbon atoms that may or may not be substituted by a hydroxyl group, a halogen atom, a cyano group, a lower alkoxy group having 1 to 3 carbon atoms, an amino group, or an acylamino group); R_2 is a hydrogen atom or a hydroxyl group.

2. A compound according to Claim 1 which is represented by the formula:



where R_2 and R' have the same meanings as defined in Claim 1.

3. A compound according to Claim 1 which is represented by the formula:

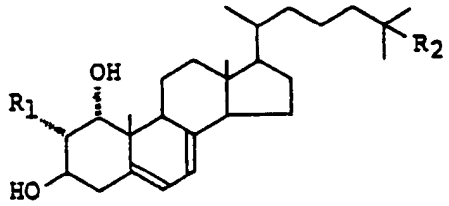


where R_2 is the same as defined in Claim 1; R_4 is a hydroxyl-substituted lower alkyl group having 1 to 7 carbon atoms.

4. A compound according to Claim 1 to 3 wherein R_2 is a hydrogen atom.

5. A compound according to Claim 1 to 3 wherein R_2 is a hydroxyl group.

6. A process for producing a 1α-hydroxy vitamin D_3 derivative of the formula I according to claim 1 by illuminating a provitamin D_3 derivative of the formula:



(where R_1 and R_2 are the same as defined above) with ultraviolet radiation, and subjecting the irradiated derivative to thermal isomerization.

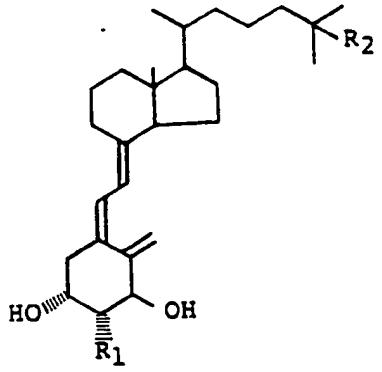
7. A 1α-hydroxy vitamin D_3 derivative of the formula I according to claims 1 to 5 for use as a pharmaceutically active agent.

8. A 1α-hydroxy vitamin D_3 derivative of the formula I according to claims 1 to 5 for use in the treatment of tumors.

9. A 1α-hydroxy vitamin D_3 derivative of the formula I according to claims 1 to 5 for use in the treatment of calcium dysbolism-caused diseases.

Patentansprüche

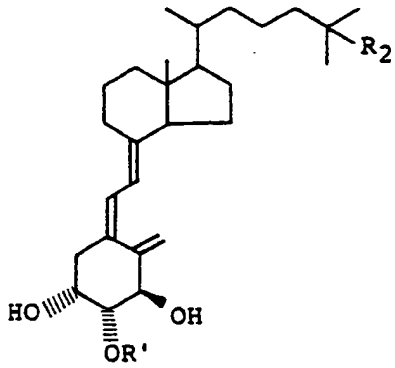
1. Ein 1α-Hydroxy-Vitamin D_3-Derivat der Formel I:



(I)

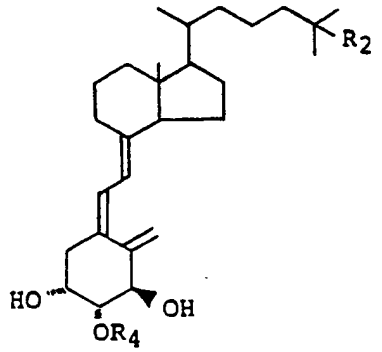
in der R_1 eine Hydroxylgruppe, eine Aminogruppe oder den Rest OR' bedeutet (in dem R' einen Niederalkylrest mit 1 bis 7 Kohlenstoffatomen darstellt, der gegenbenenfalls durch eine Hydroxylgruppe, ein Halogenatom, eine Cyangruppe, einen Niederalkoxyrest mit 1 bis 3 Kohlenstoffatomen, einen Amino- oder Acylaminorest substituiert sein kann), und R_2 ein Wasserstoffatom oder eine Hydroxylgruppe darstellt.

2. Verbindung nach Anspruch 1 mit der Formel:



in der R_2 und R' die in Anspruch 1 angegebenen Beduetungen haben.

3. Verbindung nach Anspruch 1 mit der Formel:

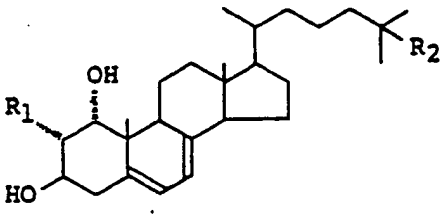


in der R_2 die in Anspruch 1 angegebene Bedeutung hat, und R_4 einen hydroxylsubstituierten Niederalkylrest mit 1 bis 7 Kohlenstoffatomen darstellt.

4. Verbindung nach Anspruch 1 bis 3, in der R_2 ein Wasserstoffatom ist.

5. Verbindung nach Anspruch 1 bis 3, in der R_2 eine Hydroxylgruppe darstellt.

6. Verfahren zur Herstellung eines 1α-Hydroxy-Vitamin D_3-Derivats der Formel I nach Anspruch 1, bei dem man ein Provitamin D_3-Derivat der Formel



(in der R_1 und R_2 die oben angegebenen Bedeutungen haben) ultravioletter Strahlung aussetzt und das bestrahlte Derivat thermischer Isomerisierung unterwirft.

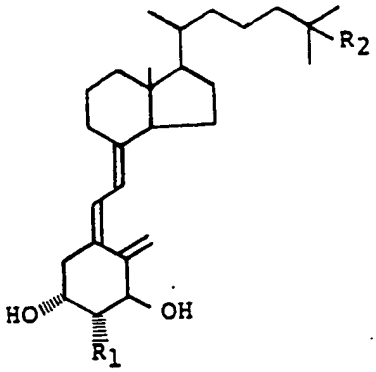
7. Ein 1α-Hydroxy-Vitamin D_3-Derivat der Formel I nach Anspruch 1 bis 5 zur Verwendung als pharmazeutischer Wirkstoff.

8. Ein 1α-Hydroxy-Vitamin D_3-Derivat der Formel I nach Anspruch 1 bis 5 zur Verwendung bei der Behandlung von Tumoren.

9. Ein 1α-Hydroxy-Vitamin D_3-Derivat der Formel I nach Anspruch 1 bis 5 zur Verwendung bei der Behandlung von durch Calcium-Stoffwechselstörungen verursachten Krankheiten.

Revendications

1. Dérivé de la 1α-hydroxy vitamine D_3 de formule I:

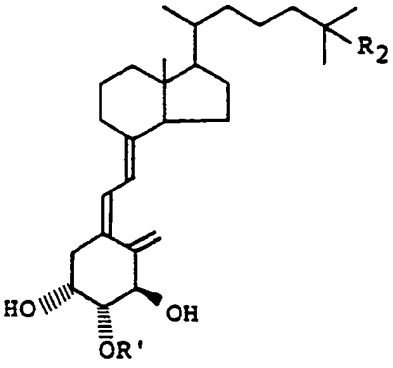


(I)

où R_1 est un radical hydroxyle, un radical amino ou le radical OR' (où R' est un radical alcoyle inférieur de 1 à 7 atomes de carbone qui peut être substitué ou non par un radical hydroxyle, un atome d'halogène, un radical cyano, un radical alcoxy inférieur de 1 à 3 atomes de carbone, un radical amino ou un radical acylamino); et

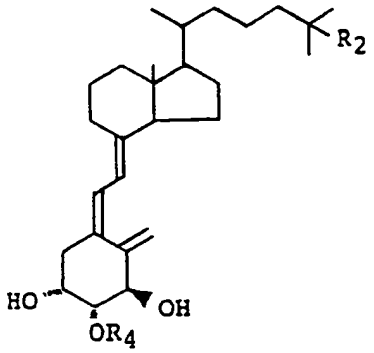
R_2 est un atome d'hydrogène ou un radical hydroxyle.

2. Composé suivant la revendication 1 de formule:



où R_2 et R' ont les mêmes significations que celles définies dans la revendication 1.

3. Composé suivant la revendication 1 de formule:

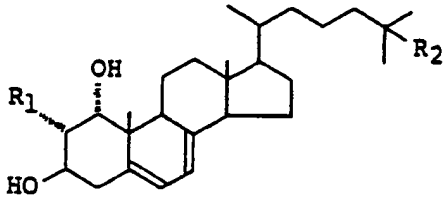


où R_2 est tel que défini dans la revendication 1 et R_4 est un radical alcoyle inférieur hydroxy-substitué comptant 1 à 7 atomes de carbone.

4. Composé suivant les revendications 1 à 3, dans lequel R_2 est un atome d'hydrogène.

5. Composé suivant les revendications 1 à 3, dans lequel R_2 est un radical hydroxyle.

6. Procédé de préparation d'un dérivé de la 1α-hydroxy vitamine D_3 de formule I suivant la revendication 1, par irradiation d'un dérivé de la provitamine D_3 de formule:



(où R_1 et R_2 sont tels que définis ci-dessus) au moyen d'un rayonnement ultraviolet et par exposition du dérivé irradié à l'isomérisation thermique.

7. Dérivé de la 1α-hydroxy vitamine D_3 de formule I suivant les revendication 1 à 5 utiliser comme agent pharmaceutiquement actif.

8. Dérivé de la 1α-hydroxy vitamine D_3 de formule I suivant les revendication 1 à 5 utiliser pour le traitement de tumeurs.

9. Dérivé de la 1α-hydroxy vitamine D_3 de formule I suivant les revendication 1 à 5 utiliser pour le traitement d'affections provoquées par un dysbolisme du calcium.